OFFICE OF NAVAL RESEARCH

CONTRACT N00014-94-C-0149

TECHNICAL REPORT 97-01

THE RED BLOOD CELL TRANSFUSION TRIGGER: HAS THE SIN OF COMMISSION NOW BECOME A SIN OF OMISSION?

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1 MAY 1997

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RUNNING TITLE: RBC TRANSFUSION TRIGGER

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This work was supported by the U.S. Navy (Office of Naval Research Contract N00014-94-C-0149), with the funds provided by the Naval Medical Research and Development Command.

The opinions or assertions contained herein are those of the authors and are not to be construed as official or reflecting the views of the Navy Department or Naval Service at large.

INTRODUCTION

Since 1983 when it became apparent that the human immunodeficiency virus (HIV) could be transmitted through blood transfusions, the number of blood transfusions administered in the United States has decreased significantly (1-7). A restrictive transfusion practice is now being employed, even though much of the reported data in support of this practice are from retrospective studies and thus incomplete (8-21).

This paper will report how anemia affects oxygen delivery, hemostasis and non-surgical blood loss, and nitric oxide production and platelet dysfunction. We will discuss normovolemic and hypovolemic anemia, as well as central blood volume and peripheral blood volume, and will report how red blood cell transfusions may affect morbidity and mortality.

The transfusion of red blood cells can increase oxygen carriage and delivery to tissues; increase carbon dioxide carriage and delivery to the lungs; regulate acid-base balance; increase red blood cell volume, plasma volume, and total blood volume; and restore hemostasis (22,23). The potential risks of a transfusion include hemolytic transfusion reactions, transfusion-related graft-versus-host disease, non-hemolytic febrile transfusion reactions, transmission of disease, immune suppression, and posttransfusion infection (5-7,22-27). Determinations about transfusion requirements are based on

patient pathophysiology; the clinical situation, whether for elective, urgent or emergency reasons; the disease for which the patient is being transfused; and whether the transfusion is required before, during, or after surgery. The patient's cerebrovascular and cardiovascular, as well as hemodynamic, pulmonary, and hematologic status are important factors to consider.

Before the potential risk of HIV infection from donor blood became known, a hematocrit value of 30% and a hemoglobin concentration of 10 g/dl served as the clinical threshold for a red blood cell transfusion, i.e., the "transfusion trigger" (28). Anemic patients with cardiopulmonary and cerebrovascular insufficiency generally were transfused to greater extents than were anemic patients without these comorbid conditions (29,30).

Oxygen carriage by the blood is determined by the hemoglobin concentration/hematocrit value and the percent saturation of the arterial blood. In anemic patients without cardiopulmonary and cerebrovascular insufficiency, an increase in blood flow will compensate for a decrease in oxygen carriage. When blood flow is impaired as a result of cardiac dysfunction, coronary artery disease, or cerebrovascular disease and failure of pulmonary function to properly oxygenate the blood, the hemoglobin concentration and hematocrit value affect morbidity and mortality (21).

The decision to transfuse or not is usually based on measurements of hematocrit value and hemoglobin concentration in

the patient's peripheral venous blood. However, these measurements do not give a true indication of the red blood cell deficit because they yield inaccurate estimates of red blood cell volume, plasma volume, and total blood volume (22,23). Accurate measurements of red blood cell volume, plasma volume and total blood volume are difficult to obtain because testing requires the use of radioactive labeling of autologous red blood cells with chromium-51 (51-Cr) or technetium-99m (99mTc) (31,32).

An accurate estimate of a patient's plasma volume can be made by using the 51-Cr or 99mTc labeling technique in conjunction with an estimate of the total body hematocrit obtained by multiplying the peripheral venous hematocrit by 0.89 in patients without splenomegaly or 1.0 for patients with massive splenomegaly (22,31,33). Radiolabeled human albumin should not be used to measure the plasma volume because it is rapidly distributed into the extravascular space in patients (31,33).

Anemia usually is defined as a reduction in the hemoglobin concentration and hematocrit value in peripheral blood. However, these measurements do not give an accurate estimate of the red blood cell deficit, nor do they tell us whether the recipient is normovolemic, hypovolemic, or hypervolemic. Anemic patients are usually hypovolemic (31). Patients with renal disease have normovolemic anemia, a condition associated with a normal blood volume, a reduced red cell volume, an increased plasma volume, and a reduced hematocrit value and hemoglobin concentration in the peripheral blood. The more common hypovolemic anemic

patient, on the other hand, exhibits reduced total blood and red blood cell volumes and normal or reduced plasma volumes, and has hematocrit values and hemoglobin concentrations that may be slightly, moderately, or markedly reduced (22,33,34); importantly, these patients may exhibit spuriously elevated peripheral blood measurements of hematocrit and hemoglobin concentration. A third type of anemia, hypervolemic anemia, observed in highly conditioned athletes, is associated with increased total blood, red blood cell, and plasma volumes, and a slightly reduced peripheral venous hematocrit value and hemoglobin concentration (35).

A red blood cell transfusion should increase the red blood cell volume, decrease the plasma volume, increase the peripheral venous hematocrit value and hemoglobin concentration in a normovolemic anemic patient, but may not produce the same response in a hypovolemic anemic patient: In the hypovolemic anemic patient, there may be increases in both plasma volume and red blood cell volume but not in the peripheral venous hematocrit and hemoglobin concentration (22,23,33,34,36). Thus, it is necessary to measure more than the peripheral venous hematocrit value and hemoglobin concentration to accurately estimate the therapeutic effectiveness of a red blood cell transfusion.

The role of red blood cells in the carriage and delivery of oxygen to tissues, carriage and delivery of carbon dioxide to the lungs, and regulation of acid-base balance is well established. However, the role of red blood cells in the regulation of plasma

volume has only recently been recognized (33,34,36). The red blood cell volume plays a role in the regulation of the plasma volume; in most patients without renal insufficiency, a reduction in red blood cell volume usually is associated with a reduction in plasma volume and total blood volume (22,23,33,34).

A hematocrit value of 21% and a hemoglobin concentration of 7 g/dl is the transfusion trigger utilized most of the time in clinical medicine, with the assumption that the patient has normovolemic anemia. However, for a patient who is actually hypovolemic anemic, these values are falsely elevated. For example, a patient with a reduction in total blood volume of 20%, a hematocrit value of 21%, and a hemoglobin concentration of 7 g/dl, is both hypovolemic and anemic (22,23,33,34). If this hypovolemic anemic patient were to become normovolemic and anemic, the total blood volume would be normal due to an increase in the plasma volume, with a resulting peripheral venous hematocrit value of 18% and a hemoglobin concentration of 6 g/dl. Hypovolemic anemic patients exhibit higher than expected hematocrit values and hemoglobin concentrations because in these patients the plasma volume does not usually increase to achieve a normovolemic anemic state (22,23,33,34).

Central Blood Volume, Peripheral Blood Volume and Total Blood Volume

The term, "normovolemic hemodilution state", commonly used by anesthesiologists and critical care physicians, is a misnomer because it reflects the central blood volume but not the total

blood volume (37). Clinicians usually assess the restoration of blood volume from measurements of mean arterial pressure; heart rate; pulmonary artery wedge pressure; cardiac output; arterial pO2, pCO2, pH; and urine output (33,38,39). These measurements assess the central blood volume but not the peripheral blood volume or the total blood volume. The peripheral blood volume refers to the volume of blood in the muscles, bones, skin, and, importantly, the gastrointestinal tract.

In anemic patients, mortality is usually associated with a failure to restore perfusion and oxygen delivery to vital organs, and morbidity with a failure to restore perfusion and oxygen delivery to both vital organs and non-vital organs such as the gastrointestinal tract and the extremities. In hypovolemic anemic patients, a reduction in perfusion to the gastrointestinal tract may produce intestinal ischemia with entry of bacteria from the gut into the circulation producing endotoxin-mediated multiple organ dysfunction (40-42).

Extensive studies in patients with traumatic injuries exhibiting hypovolemic anemia with significant reductions in red blood cell, plasma and total blood volumes have shown that although transfusions of red blood cells increased both red blood cell and plasma volumes, only minimal increases in the hematocrit value and hemoglobin concentration were observed (33,34). The increased plasma volume seen in these hypovolemic anemic patients following a red blood cell transfusion was a consequence of recruitment of extravascular proteins via the lymphatic

circulation into the systemic circulation (22,23,33,34,36). Traumatized, hypovolemic anemic patients had normal central red blood cell volumes and significantly reduced peripheral red blood cell and total red blood cell volumes (Figure 1). When red blood cells were transfused to these patients, a significant increase in peripheral red blood cell volume was observed, but no increase in the central red blood cell volume was observed during the 24-hour posttransfusion period (Figure 1) (33).

The beneficial effect of red blood cell transfusions seen in hypovolemic patients with traumatic injuries may have been a reflection of the restoration of blood volume and blood flow to the gastrointestinal tract (33,34). Studies are needed to determine how total blood volume, red blood cell volume, and plasma volume, as well as blood flow to the gastrointestinal tract and extremities, relate to mortality and morbidity in anemic patients. It is also important to learn whether perfusion of the extremities correlates with perfusion of the gastrointestinal tract in anemic patients before and after transfusion. Infrared spectroscopy may be used to assess blood flow to the extremities, and blood flow to the gastrointestinal tract may be assessed by the measurement of gastric intramucosal pH (41-44). If the perfusion of the extremities correlates with perfusion of the gastrointestinal tract, then the use of a simple non-invasive method, such as near infrared spectroscopy (NIRS), to measure peripheral blood flow to the extremities may help to determine whether a patient needs a red blood cell transfusion

and subsequently whether the transfusion is therapeutically and hemodynamically effective.

Hemostatic Effect of Red Blood Cells

Another relatively new focus on transfusion therapy concerns the role of red blood cells in hemostasis and non-surgical blood loss. Blood loss from a specific anatomic site as a result of the surgical procedure itself is referred to as "surgical" as opposed to "nonsurgical", a diffuse blood loss which is not associated with a specific anatomic site and which cannot be corrected surgically. Nonsurgical blood loss, blood viscosity and bleeding time all are influenced by the patient's peripheral venous hematocrit (45-53). A correlation has been reported between anemia and a prolonged bleeding time: when the anemia is corrected, the bleeding time is reduced (45-49,54-58). Platelet function is known to be a major determinant of bleeding time (48,59,60), and altered platelet function is believed to account for the prolonged bleeding time in anemic patients.

Data from our laboratory showing a correlation between bleeding time and nonsurgical blood loss disagree with those from some other investigators (61-63). In our study of male patients undergoing hypothermic cardiopulmonary bypass surgery, nonsurgical blood loss during the 4-hour postoperative period correlated with both the hematocrit value and the bleeding time 2 hours after the operation (63).

The administration of red blood cell transfusions and erythropoietin to correct anemia was found to curtail the

increased bleeding times in patients with renal failure and anemia (47,54-58,64,65). It also has been shown that treatment with erythropoietin or red blood cells to correct anemia in uremic patients improves platelet function (54-58). The increased bleeding time in these patients may also be associated with plasma factors present in renal failure (47,55,66,67).

Red blood cells have been shown to have a beneficial effect on platelet function in several ways. By dispersing platelets from the center of the blood vessel toward the vessel wall, red blood cells concentrate platelets near the endothelial cells of the vessel wall where they are poised to respond to injury (68). In vitro studies (69-80) have suggested that red blood cells affect platelet function by releasing ADP and that the shear-induced release of ADP from red blood cells occurs at hematocrits between 25 and 35% (74). Marcus and associates (75,80,81) have reported that platelets incubated with red blood cells in combination with collagen exhibited a greater release of beta-thromboglobulin than platelets incubated with collagen alone. These investigators also reported that red blood cells stimulate the platelets' production of thromboxane A2, which is the vasoconstrictor and platelet aggregation substance that is produced at the bleeding time site (82).

Anemia and Nitric Oxide

Anemia increases blood flow and increases shear stress on vascular endothelial cells, which stimulates the release of endothelial-derived nitric oxide (83-88). Shear stress is a

product of the shear rate and whole blood viscosity. With anemia, shear rate is increased, but blood viscosity is reduced; yet, shear stress is increased over the usual range of anemic hematocrits. Increased shear stress can have both pro- and anti-thrombotic effects. Increased shear stress increases platelet aggregation, and red blood cells augment shear-dependent platelet aggregation (69-74). An increase in shear stress also results in the release of ADP from red cells, which further potentiates shear-induced platelet aggregation (72-80). By contrast, the production of nitric oxide resulting from increased shear stress on endothelial cells stimulates platelet guanylyl cyclase activity, increases the platelet cGMP level, and inhibits platelet function (88-92). What we need to learn is whether or not nitric oxide inhibits platelets more than ADP stimulates them under these conditions of anemia-induced increases in shear stress.

The mechanisms by which anemia promotes the increase in blood flow and the inhibition of platelet function by nitric oxide are as yet unclear. Hemoglobin is an important nitric oxide scavenger, and its interaction with nitric oxide has been known since 1935 (93,94). Hemoglobin avidly binds nitric oxide, with an affinity much higher than that for either oxygen or carbon monoxide. A reduction in the number of red blood cells reduces the amount of hemoglobin in the vasculature available to bind nitric oxide. Anemia also reduces the blood viscosity, increases blood flow, and increases shear stress on the

endothelial cells, which increases endogenous nitric oxide production. Anand and associates (95) have suggested that the increase in forearm blood flow accompanying anemia is a consequence of the reduced availability of hemoglobin within the red blood cells to bind to nitric oxide. It is more likely that the hemodynamic consequences of anemia are directly responsible for the increased elaboration of nitric oxide that accompanies anemic states (88), particularly given that nitrosylhemoglobin is undetectable in whole blood except under conditions of augmented nitric oxide production such as septic shock.

Whole blood viscosity is directly related to hematocrit (the higher the hematocrit the higher the whole blood viscosity) and inversely related to the cardiac output (the higher the whole blood viscosity the lower the cardiac output) (Figure 2) (28,83,96). Relative shear stress is increased at both low and high hematocrit values: at low hematocrit values, shear stress is increased owing to an increase in shear rate disproportionate to the decrease in viscosity; at high hematocrit values, shear stress is increased owing to an increase in viscosity disproportionate to the decrease in shear rate (Figure 3). By modelling these parameters, a minimum relative shear stress value is observed at an hematocrit value between 30 and 35% (Figure 3, Appendix A). Thus, if the hemodynamic and hemostatic abnormalities accompanying anemia are attributable primarily to shear stress-induced nitric oxide release from the endothelium, it would seem logical that transfusing red blood cells to the 30

to 35% hematocrit range would minimize the development of a high cardiac output state, platelet dysfunction, and a bleeding tendency (Figures 2 and 3). The effect of specific hematocrit values on whole blood viscosity and on shear stress must be determined in order to assess the effect of nitric oxide on vasodilation of blood vessels and inhibition of platelet function.

Hemodiluted patients have reduced hematocrit values and hemoglobin concentration levels, decreased platelet counts, and reduced clotting protein levels. In these patients, the transfusion of red blood cells alone may be adequate to reduce non-surgical blood loss without the need to transfuse platelets or fresh frozen plasma. In anemic patients, transfused red blood cells may bind the excess nitric oxide in blood and, more importantly, transfused red blood cells will increase blood viscosity, reduce shear rate, and optimally reduce shear stress which will decrease endogenous nitric oxide production by the endothelial cells. Prospective, randomized studies should be instituted to investigate the effect of the hematocrit and hemoglobin concentration on the restoration of hemostasis in anemic patients, and on the reduction of non-surgical blood loss associated with cardiopulmonary bypass surgery, vascular surgery, general surgery, and resuscitation following trauma.

Transfusion Trigger

With the current practice of relying solely on measurements of peripheral hematocrit level and hemoglobin concentration to

identify the red blood cell transfusion trigger, many patients may be deprived of transfusion therapy that may help to reduce morbidity and mortality.

When trying to interpret published data on the transfusion trigger, it is important to understand that most patients requiring transfusions are hypovolemic and anemic and thus exhibit false increases in hematocrit levels and hemoglobin concentrations. Therefore, these measurements should not be the only consideration in defining the transfusion trigger.

In recent years, the clinical use of erythropoietin to treat normovolemic anemic patients with renal disease has resulted in a considerable improvement in the well-being of these patients (97). Erythropoietin is usually administered to normovolemic anemic patients with renal disease to achieve a hematocrit value of 30 to 35% and hemoglobin concentration of 10 to 12 g/dl. Human recombinant erythropoietin is also recommended for the reduction of allogeneic blood transfusions in surgical patients. Human recombinant erythropoietin is recommended for anemic patients with hemoglobin concentrations of greater than 10 g/dl and less than 13 g/dl undergoing elective surgery and patients at high risk for significant perioperative blood loss (98).

Because of the limitations of the hematologic and hemodynamic measurements, clinical judgment should be the deciding factor in determining the need for red blood cell transfusions. Tachycardia, shortness of breath, pallor, decreased tissue turgor, postural hypotension, light-headedness-

dizziness, decreased appetite, weakness, and fatigue are important signs and symptoms to be taken into account. There are even some instances in which the patient's input should be considered. There have been instances in which knowledgeable patients have suggested that they might benefit from a red blood cell transfusion, only to be discouraged by their physician. A patient properly apprised of the potential risks and benefits of a transfusion should be allowed to play a role in this important decision.

For thousands of years it was a common belief among physicians that blood letting was a useful way of treating a wide variety of illnesses, a belief that persisted despite the common sense observations of a few observant physicians that this form of treatment made the patient worse not better (99). Indeed, the first recorded instance of a successful blood transfusion was in a fifteen-year-old boy who was moribund from twenty successive blood lettings over a two-week period but who was immediately revived following transfusion (100). The present policy of allowing sick patients, particularly elderly sick patients, in the perioperative period to develop greater and greater degrees of anemia without correction by blood transfusion may some day receive the same final harsh verdict of history that blood letting as therapy finally received a hundred years ago (99). Has the sin of commission now become the sin of omission? We believe so.

SUMMARY

The benefits of an hematocrit range of 30 to 35% include improved oxygen delivery and enhanced hemostasis, which will help minimize complications in patients at high risk for ischemia and perioperative non-surgical bleeding. In these settings, the conservative transfusion practice using a lower hematocrit range should be replaced with a more aggressive approach. The known risks of blood transfusion would appear to be sufficiently low and the benefits sufficiently high to justify maintaining a hematocrit value of at least 30%. An even higher hematocrit value of 35% may be desirable in patients who have overt cardiopulmonary disease or who are at high risk for myocardial ischemia. Many retrospective studies have been conducted to persuade us that a conservative transfusion trigger is a safe and prudent practice, but retrospective studies are not what we need. What is needed is a series of well-designed, prospective, randomized trials to evaluate the impact of a more aggressive transfusion policy on perioperative mortality, morbidity, and non-surgical bleeding in patients with known cardiopulmonary disease or who are at high risk for myocardial and cerebrovascular ischemia.

ACKNOWLEDGMENTS

The authors acknowledge the editorial assistance of Ms. Cynthia A. Valeri and the secretarial assistance of Ms. Marilyn Leavy.

FIGURE LEGENDS

FIGURE 1. The total, central, and peripheral red blood cell volume (RCV) measured prior to and following the transfusion of 3 to 5 units of preserved red blood cells in seven patients with traumatic injuries (ADA = automated differential agglutination). (Reprinted with permission from C.R. Valeri, M.D. Altschule. The Hypovolemic Anemia of Trauma: The Missing Blood Syndrome. CRC Press, Inc., Boca Raton, FL, 1981, p. 98).

FIGURE 2. The relation between normalized whole blood viscosity and hematocrit and between normalized cardiac output and hematocrit. The data for cardiac output were obtained from references 101-103 and cumulatively analyzed to derive the fitted curve presented in this figure.

FIGURE 3. The theoretical relation between relative shear stress and hematocrit.

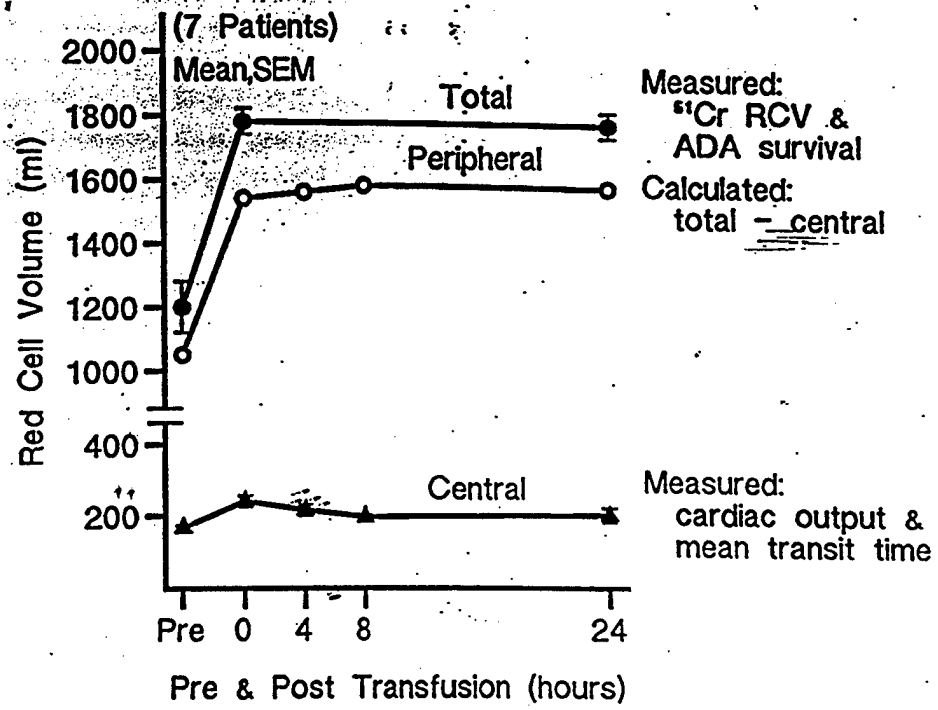

FIGURE 1

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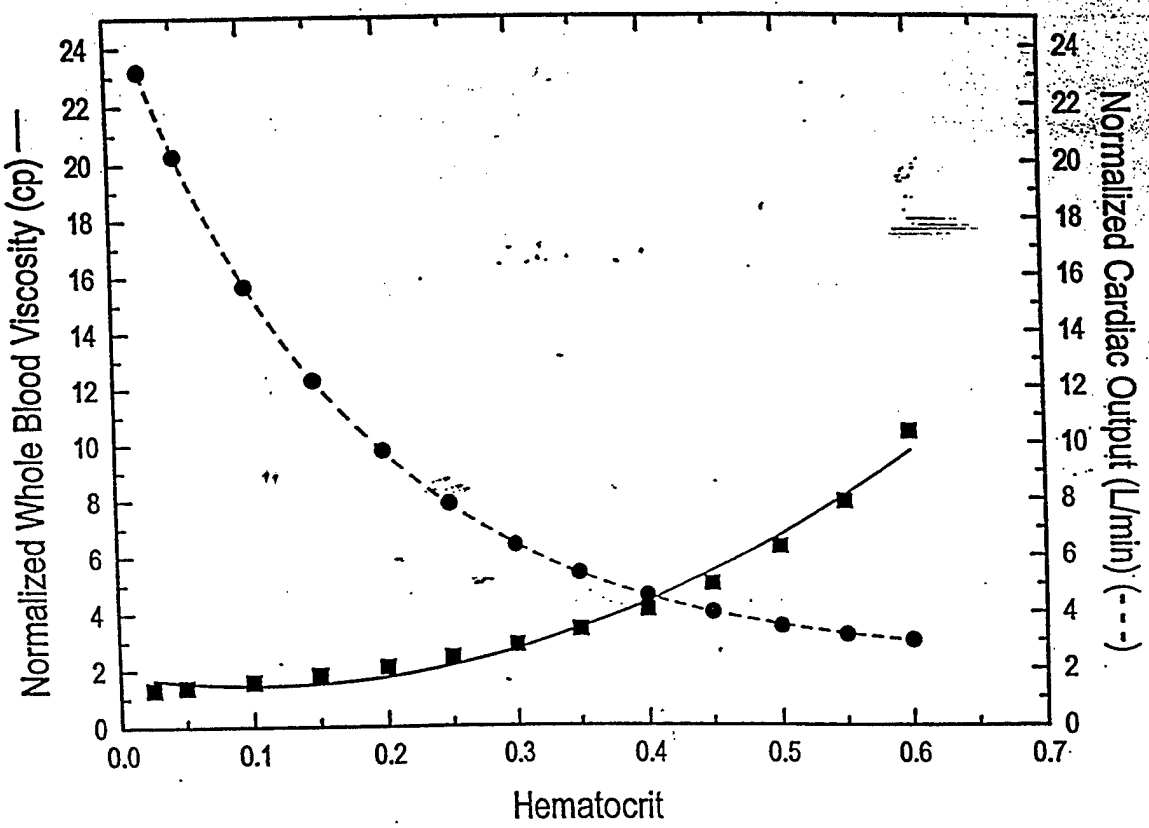

FIGURE 2

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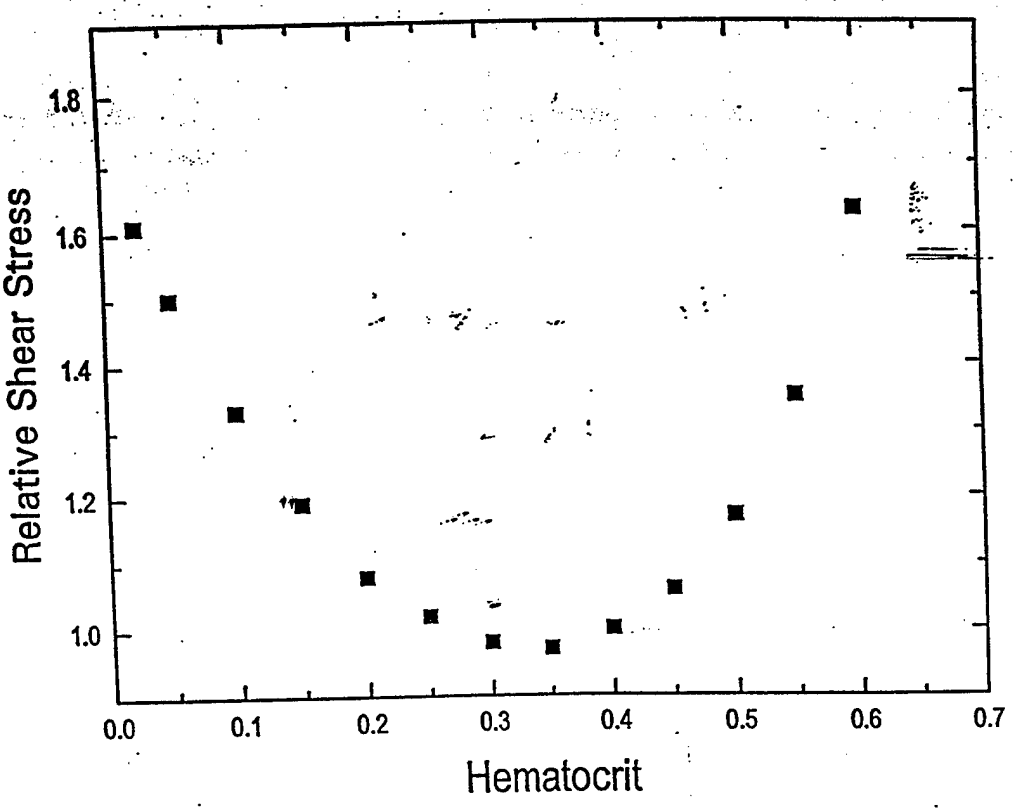

FIGURE 3

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APPENDIX A

A model of the relationship between hematocrit and shear stress is derived from the following equations:

$$\text{Shear rate} = 4Q/\pi R^3$$

where Q is volumetric flow and R is the radius of a blood vessel.

Shear stress = $\tau = \eta v$ = shear rate X whole blood viscosity

$\eta = \eta_{plasma}\ (1 - T\kappa \text{ X hct})^{-2.5}$ where T is Taylor's factor, κ is a plasma trapping coefficient, and $T\kappa = 0.956$; $\eta_{plasma} = 1.229$ cp. The calculation of whole blood viscosity by this method assumes high shear rate conditions, where viscosity is independent of shear.

Thus, the shear stress at any given hematocrit is given by

$$r = 4\eta Q/\pi R^3$$

Shear stress relative to that at a normal hematocrit (0.4) yields the following equation:

$$T_{Rel} = T_{Hct=x}/T_{Hct=0.4} = (\eta_{Hct=x} Q_{Hct=x}) / (\eta_{Hct=0.4} Q_{Hct=0.4})$$

The relationship between hematocrit and cardiac output can be fitted to an exponential of the following empirical form:

$$Q = CO = 4.62 + 11.68_e{}^{[-(Hct-0.0294)/0.0351)]}$$

Thus, Q at an hematocrit of 0.4 = 4.626 L/min. Similarly, η at an hematocrit of 0.4 = 4.1 cp.

With these values,

$$T_{Rel} = (\eta_{Hct=x}/Q_{Hct=x})/18.97 = 0.065(1 - T\kappa \text{ x hct})^{-2.5} \text{ X } [4.62 + 11.68e^{[-(Hct-0.0294)/0.0351)]}$$

when this equation is solved for a range of hematocrit values, it yields a function with a minimum value, as shown in Figures 2 and

3. The relationship between hematocrit and shear stress is a consequence of two opposing effects: the inverse relationship between cardiac output and hematocrit and the direct relationship between blood viscosity and hematocrit. The interplay of these two opposing effects accounts for the optimal (minimal) hematocrit required to minimize shear stress on the endothelium and the elaboration of nitric oxide with its resulting vasodilatory and platelet inhibitory consequences.